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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,069	03/30/2001	Kenneth T. Wheeler	9151-6	8239

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 06/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,069	WHEELER ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *22 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-34* is/are pending in the application.

4a) Of the above claim(s) *9,10 and 12-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 4-7, 11, 33-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed 3/22/04 has been entered

2. The reply filed on 3/22/04 is not fully responsive to the prior Office Action because of the following omission(s) or matter(s): Applicant has not addressed Examiners arguments pertaining to Sequence Rules Compliance, stated on page 2, subsection 4, of the Office Action12/17/03. This application fails to comply with the sequence rules, 37 CFR 1.821-1.825. Nucleotide and polypeptide sequences must be identified with the corresponding SEQ ID NO. Title 37, Code of Federal Regulations, Section 1.821 states "reference must be made to the sequence by use of the assigned identifier", the identifier being SEQ ID NO. Figures 3 and 5 contain sequences, which have not been identified by SEQ ID NO:. All sequences in Figure 2 and 5 must be identified by their corresponding SEQ ID NO:. Correction is required.

Claim Rejections Under 35 USC § 101 and 35 USC § 112, 1st paragraph

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6 and 7 remain rejected under 35 U.S.C. 101, for reasons given in the Office Action dated 7/12/03, and for the reason given below, because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Amended claims 1, 4, 5, 11 and newly added claims 33-34 are also rejected under 35 U.S.C. 101, for the reasons below. The rejection under 35 U.S.C. 101, provided in the Office Action dated 7/12/03 is also applied to amended claims 1, 4, 5, 11 and newly added claims 33 and 34 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

3. **Response to Applicants Arguments**

Applicant argues the case clearly states an adequate utility consistent with the guidelines set forth in the Utility Examination Guidelines. Applicants' arguments are summarized below:

The sigma receptors are useful as markers in the non-invasive detection and visualization of a wide variety of tumors. Furthermore, the specification states with regard to the sigma 1B receptor, because this new variant exhibits σ2-like binding, it is useful in the screening of compounds useful in the detection of the proliferation state of tumors, as well as in other uses. The new $\sigma 1\beta$ variant finds particular use in the non-invasive diagnosis of cancer and more particularly in the diagnosis of proliferative cancer cells. The compounds of the present application allows for such uses as diagnostic compounds for the imagining of tumor cells. These compounds also are useful as therapeutics for the treatment of cancer and other disorders of cell proliferation. These ligand compounds of the present application are also useful in methods of determining the proliferative status of a tumor. Furthermore, the methods and compositions of the present invention are also useful in relation to non-cancer disorders of cell proliferation. These diseases include, but are not limited to, benign tumors, hyperplasias, hyperpigmentation of the skin, psoriasis, and any other disorder wherein cell proliferation is uncontrolled, and control, diagnosis, or imaging of such

proliferation is desired. Applicants also note that the $\sigma 1\beta$ receptor exhibits $\sigma 2$- like binding. As such, "methods for determining the proliferative state of a cell by determining cell's ability to bind $\sigma 2$ receptors may now be carried out using a cell's ability to bind $\sigma 1\beta$". Applicants further note that these methods for determining the proliferative status of cancer cells are carried out by determining the ability of proliferative cells to bind $\sigma 1$ and $\sigma 1\beta$ ligands, respectively. The ratio of $\sigma 1\beta$ to $\sigma 1$ density on a cell is an indicator of the proliferative state of the cell. Applicants further note that σ receptors have been defined as nonopiate, nondopaminergic, and nonphencyclidine receptors based on their ligand binding characteristics. Thus, the utilities of the present invention are specific, substantial, and credible, and clearly satisfy the requirements of 35 U.S.C. 101 .Hence, it is respectfully submitted that this rejection should be withdrawn.

Applicant's arguments have been fully considered but are not found persuasive.

The specification discloses the $\sigma 1\beta$ receptor of SEQ ID NO: 2 is encoded by the polynucleotide of SEQ ID NO: 1. Mach et al (see IDS, Cancer Research Vol. 57, 1546-161, 1997) disclose, although the expression of $\sigma 1$ and $\sigma 2$ receptors is heterogeneous, their function is unknown (see Abstract). Malliga et al (see IDS, The Journal of pharmacological and Experimental Therapeutics, Vol. 289, page 251-260) disclose the biochemical and pharmacological profiles of these receptors differ markedly, indicating species and cell type dependent differential expression of various subtypes of σ receptors in immune cells. (See page 252, column 1, first paragraph). Further WO 97/34792 (see IDS) also discloses the function of $\sigma 2$ is unknown (see page 1). The $\sigma 1\beta$ receptor of instant invention is expressed in a wide variety of tissues, normal and cancerous. Therefore based on the art and the disclosure, the functionality of claimed $\sigma 1\beta$ receptor of SEQ ID NO: 2 is unknown. Members of the $\sigma 1$ receptor family are also highly divergent in their effects and ligand specificity. Based on the homology data of the $\sigma 1$ receptor family and the general classification into the superfamily of $\sigma 1$ receptor family, the specification discloses the claimed $\sigma 1\beta$ receptor is useful for detecting,

preventing and/or treating diseases associated with cancer. There is no clear nexus between the treatable diseases/disorders and use of claimed $\sigma 1\beta$ receptor. Even if a test compound in an assay for drug screening affects the expression of Applicant's individual $\sigma 1\beta$ receptor, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. The ratio of $\sigma 1$ to $\sigma 1\beta$ density that may be an indicator of proliferate state of the cells is not disclosed. Even if the ratio of $\sigma 1$ to $\sigma 1\beta$ density varies in cells, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. There is no disclosure of the ratios of $\sigma 1$ to $\sigma 1\beta$ that would indicate proliferate state. For example, if the ratio of $\sigma 1$ to $\sigma 1\beta$ is 2:1, 1:2, 1.1:1 or 1:1.1, what is the interpretation for the result? None is provided. Given this consideration, and those stated above, the individually claimed method of using $\sigma 1\beta$ receptor has no "well-established" use. The artisan is required to perform further experimentation on the claimed $\sigma 1\beta$ receptor itself in order to determine to what "use" any information regarding this protein could be put.

In light of the specification the skilled artisan can not come to any conclusions as to the function of claimed nucleic acid encoding the $\sigma 1\beta$ receptor of SEQ ID NO: 2 or variants thereof.

The utility of claimed protein cannot be determined solely from homology to the proteins known in the art because the art does not provide teaching stating that all proteins disclosed have the same activity, same effects, the same ligands and are involved in the same disease states. In light of the specification and art the skilled artisan cannot come to any conclusions as to the function of the protein encoded by the

claimed nucleic acid. There is no disclosure provided within the instant specification on what specific function the protein of SEQ ID NO: 2 possesses, or how to specifically assay for such, ligands that bind or promoters that activate. There are no disease states disclosed that are directly related to said protein dysfunction. The specification fails to disclose, what disease is associated with claimed $\sigma 1\beta$ receptor dysfunction, or what drugs affect a specific claimed receptor function. The claimed $\sigma 1\beta$ receptor may have utility in the future, when it has been further characterized (e.g. its dysfunction or function correlated with a disease state) and its endogenous ligand characterized and functionality determined. The inclusion in the family of σ receptor does not constitute either a specific and substantial asserted utility or a well-established utility for that particular $\sigma 1\beta$ receptor. This is analogous to all proteins/nucleic acid of σ receptor being used as markers on a gel.

The specification discloses that the claimed receptors are useful in screening but the specification does not disclose what claimed $\sigma 1\beta$ receptor specifically regulates or what specific disease the claimed $\sigma 1\beta$ receptor is a target for. Further the functional effects of ligand binding may remain uncertain even after extensive experimentation. The ordinary artisan can only speculate on the utility for the ligand for $\sigma 1\beta$ receptor. A utility for orphan $\sigma 1\beta$ receptor cannot be assigned without knowledge of what disease is associated with the claimed $\sigma 1\beta$ receptor dysfunction or what drugs/ligands effect a specific claimed $\sigma 1\beta$ receptor function. The superfamily of σ receptor is highly divergent in their effects and compound specificity. The utility of the claimed $\sigma 1\beta$ receptor cannot be implicated solely from homology to known $\sigma 1$ receptors or their protein domains

because the art does not provide any teaching stating that all members of family of $\sigma 1$ receptors must have the same effects, the same ligands and be involved in the same disease states. In fact, the art discloses evidence to the contrary.

It can be argued that the claimed $\sigma 1\beta$ receptor is a useful tool and can be used as a reagent or as a molecular target in the diagnosis and treatment of the claimed $\sigma 1\beta$ receptor mediated disorders. All members of the $\sigma 1$ receptor family have a utility in selectively screening of candidate drugs that target $\sigma 1$ receptors. However, for a utility to be "well-established" it must be specific and substantial. In this case, all $\sigma 1$ receptors are in some combination useful in the selectively screening of candidate drugs that target $\sigma 1$ receptors. However, the particulars of screening of candidate drugs that target the claimed $\sigma 1\beta$ receptor is not disclosed in the instant specification. Neither the candidate drugs nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to SEQ ID NO: 1 and 2. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed protein for screening compounds that are a target for claimed $\sigma 1\beta$ receptor is only useful in the sense that the information that is gained from the assay is dependent on the effect it has on the protein, and says nothing with regard to the activity each individual member of the $\sigma 1\beta$ receptor family. Again, this is a utility, which would apply to virtually every member of a

general class of materials, such as any collection of proteins or DNA. Even if a test compound in an assay for drug screening affects the expression of Applicant's individual $\sigma 1\beta$ receptor, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed method of using $\sigma 1\beta$ receptor has no "well-established" use. The artisan is required to perform further experimentation on the claimed $\sigma 1\beta$ receptor itself in order to determine to what "use" any information regarding this protein could be put.

With regard to diagnosis of disease, in order for a polynucleotide or protein to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed $\sigma 1\beta$ receptor and a disease or disorder. The presence of claimed $\sigma 1\beta$ receptor in tissue is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed $\sigma 1\beta$ receptor and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed $\sigma 1\beta$ receptor to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed $\sigma 1\beta$ receptor is either present only in, e.g. cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of claimed $\sigma 1\beta$ receptor as a diagnostic for a disease. However, in the absence of any disclosed

relationship between the claimed $\sigma 1\beta$ receptor and any disease or disorder and the lack of any correlation between the claimed $\sigma 1\beta$ receptor with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Further, $\sigma 1$ receptor family belongs is a family in which the members have divergent functions based on which tissues the protein is expressed or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific and substantial utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. The diversity of the $\sigma 1$ receptor family has already been described. Without some common biological activity for the family members, a new member would not have a specific or substantial utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities, which may be related to tissue distribution, but there is no evidence that the claimed compounds share any one of a diverse number of activities. That is, no

activity is known to be common to all members. To argue that all the members can be used for drug screening, toxicology testing and diagnosis, is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use.

Without knowing a biological significance of the claimed $\sigma 1\beta$ receptor, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a "real world" manner based on the diversity of biological activities possessed by the $\sigma 1$ receptor family. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (Evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art

would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The assertion that the claimed invention has utility in drug screening, drug development and disease diagnosis, do not meet the standards for a specific, substantial or well-established utility for reasons set forth above. None of the utilities identified have been demonstrated to be specific to the polypeptide encoded by the nucleic acid of SEQ ID NO: 1. One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of the polypeptide SEQ ID NO: 2 or the polynucleotide of SEQ ID NO: 1. Applicant has failed with respect to claimed $\sigma 1\beta$ receptor to describe the family of $\sigma 1$ receptors in enough detail to show, by a preponderance of the evidence, that the polypeptide of SEQ ID NO: 2 or the polynucleotide of SEQ ID NO: 1 or variants thereof has any substantial use. The record shows that the family of proteins having $\sigma 1$ receptor domains is diverse), and has such a broad definition, that a "common utility" cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner,* the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention.

The use of the claimed invention for toxicology testing, drug discovery, and disease diagnosis are not substantial utilities. The question at issue is whether or not the broad general assertion that the claimed $\sigma 1\beta$ receptor might be used for some diagnostic application in the absence of a disclosure of which diagnostic application would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

The rejection under § 101 follows *Brenner v. Manson*. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of

action. A rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967). Further since the claimed $\sigma 1\beta$ receptor (TMP) has no utility, methods of its use are also rejected for lack of utility.

35 U.S.C. 112, first paragraph

4. Claims 6 and 7 remain rejected under 35 U.S.C. 112, first paragraph for reason given in the Office Action dated 7/12/03, and for the reason given below. Amended claims 1, 4, 5, 11 and newly added claims 33-34 are so rejected under 35 U.S.C. 112, first paragraph for the reasons given below. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed $\sigma 1\beta$ receptor polynucleotide (SEQ ID NO:1) encoding the polypeptide of SEQ ID NO:2, or variants thereof. Further experimentation is necessary to attribute a utility to the claimed nucleic acid encoding the $\sigma 1\beta$ receptor and variants thereof.

Applicants argue because of the arguments provided under 35 U.S.C. 101, the amendments that remove the hybridization issues and the inclusion of sequence homology language into the claims the rejection under 35 U.S.C. 112, first paragraph should be withdrawn. Applicant's arguments have been fully considered and found persuasive in part. The rejection 35 U.S.C. 112, first paragraph pertaining to the hybridization issues is withdrawn. Claims 1, 4-7, 11, 33 and 34 are 35 rejected under

U.S.C. 112, first paragraph because claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above.

5. Further, even if claims 1, 5-7, 11, 33 and 34 are found to have utility under 35 U.S.C. 101 they fail to comply with the enablement requirement under 35 U.S.C. 112, first paragraph. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to:

a) Isolated polynucleotide that has at least 85% homology to the polynucleotide of SEQ ID NO:1.

b) Isolated polynucleotide that has at least 85% homology to the polynucleotide encoding the $\sigma 1\beta$ receptor SEQ ID NO:2.

c) An expression vector comprising the polynucleotide of a) or b).

d) Cell comprising the expression vector of c).

e) Method for producing a protein comprising the amino acid sequence of SEQ ID NO:2, or comprising a fragment thereof, said method comprising culturing a host cell comprising an expression vector comprising at least a fragment of the polynucleotide sequence of SEQ ID NO:1 encoding a $\sigma 1\beta$ receptor under conditions suitable for the expression of the protein

f) A transformed host cell comprising the polynucleotide of a) or b)

h) The method according to e) wherein the fragment comprises 20 nucleotides.

A review of *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) clearly points out the factors to be considered in determining whether a disclosure would require undue experimentation and include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors are considerations when determining the whether undue experimentation would be required to use the claimed invention.

(1) The quantity of experimentation necessary

Even though the skill of the artisan in the art of molecular biology is high, undue experimentation is required to make functional $\sigma 1\beta$ receptor variants. The specification has not disclosed the use of non-functional variants. The claims encompass billions of variants (see the rejection under Written Description for the algorithm that can be uses to determine the variants) with no specific activity.

(2) The amount of direction or guidance presented

The production of polynucleotides that encode functional $\sigma 1\beta$ receptors variants, encompassed by the claims, requires knowledge of a common property or critical technical feature of the genus claimed. The production of functional variants requires that conserved regions, which are critical to the structure, and function of the protein be known. There is no disclosure of said conserved regions, which are critical to the structure, and function of the protein. There is no description of the sites at which variability may be tolerated. There is no information regarding the relationship of

structure to function. There is no clear evidence of the activity possessed by the claimed genus of nucleic acid molecules encoding variant $\sigma 1\beta$ receptor polypeptides. Substitutions/addition/deletions that result in active variants are not disclosed. Substitutions/addition/deletions that are detrimental to $\sigma 1\beta$ receptor variant activity are not disclosed. A person skilled in the art would not know how to make and use the claimed invention so that it would operate as intended without undue experimentation.

(3) The presence or absence of working examples

The disclosure fails to provide a representative number of species and structural data to enable the production and use of the genus as broadly claimed.

(4) The nature of the invention

Isolated polynucleotide encoding $\sigma 1\beta$ receptor variants is claimed. The claims encompass billions of variants with no specific defined activity.

(5) The state of the prior art

The genus of $\sigma 1$ has diverse functions and compound specificity (disclosed above). Because of the lack of guidance in the prior art and current application, one skilled in the art could not predict if the variants $\sigma 1\beta$ receptor would have the same functionality as the protein disclosed in SEQ ID NO:2, since no activity is disclosed It can also not be predicted which variants contain the domain(s) of SEQ ID NO:2, containing the critical special technical feature of the claimed $\sigma 1\beta$ receptor, since no critical special technical feature is disclosed in the specification or prior art. Prior art does not disclose the production of functional $\sigma 1\beta$ receptor variants.

(6) the relative skill of those in the art

Although skill in the art is high, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides that would enable the production of functional variants encoding $\sigma 1\beta$ receptors.

(7) The predictability or unpredictability of the art

Prior art discloses the complexity of producing functional variants. It is also difficult to predict function from structure. Bowie et al (Science, March 16, 1990, Vol. 247, pages 1307-1310) discloses that the function of a protein cannot be predicted from the sequence of a protein (page 1310, column). Mutating proteins by amino acid substitutions can have a dramatic effect on function. The location of the mutation and the type of amino acid substituted is critical for protein functionality (page 1037, column 2). For example, replacing the Asp in the catalytic triad of trypsin with Asn results in a 10^4-fold reduction in activity (page 1307, column 2). Based on the disclosure of Bowie it can be concluded that mutations in residues that are required for structure formation or stability can have dramatic effects on activity.

(8) The breadth of the claims

The claims encompass nucleic acid comprising variants of SEQ ID NO:1 and encoding variants of the polypeptide of SEQ ID NO:2. The variants may be completely unrelated, structurally and functionally to the protein encoded by the nucleic acid of SEQ ID NO:1. The claims are drawn to an orphan $\sigma 1\beta$ receptor. Neither the claims nor the specification disclose what specific biological activity is associated with the claimed

$\sigma 1\beta$ receptor or what specifically classifies a protein as a $\sigma 1\beta$ receptor. Therefore, nucleic acid encoding unrelated and inactive proteins are encompassed by the claims. The specification does not disclose how to produce active variants or how to use inactive ones encoded by polynucleotides that have, for example, at least 85% homology to the polynuclotide of SEQ ID NO:1, comprise fragments of the polynucleotide of SEQ ID NO:1, or encode fragments of the polypeptide of SEQ ID NO:2.

Therefore, many of the polynucleotides that have at least 85% homology to the polynuclotide of SEQ ID NO:1 may be unrelated to the nucleic acid encoding the polypeptide of SEQ ID NO:2. Also, many of the polynucleotides that have at least 85% homology to the polynuclotide encoding the polypeptide of SEQ ID NO:2 may be unrelated to the nucleic acid of SEQ ID NO:1. The specification does not disclose how to produce active variants. The specification does not disclose how to use inactive polypeptides encoded by claimed nucleic acid molecule. Also, the specification does not disclose how to use unrelated polypeptides (i.e. functionally unrelated to $\sigma 1\beta$ receptor) encoded by claimed nucleic acid molecule. The claimed nucleic acid encodes a $\sigma 1\beta$ receptor whose functionality has not been disclosed. Neither the claims nor the specification disclose what specific biological activity is associated with the claimed $\sigma 1\beta$ receptor. There is no disclosure of how to assay variants since the natural ligand, compound transported and function of the claimed invention is unknown.

Therefore, undue experimentation is necessary to make and identify the polypeptides with the structural and functional features of instant invention. There is a

the lack of direction/guidance presented in the specification regarding the synthesis, identification, purification, isolation and characterization of the variants polypeptides encoded by the claimed polynucleotides. Due to the unpredictability of the effects of mutation on the structure and function of proteins, and the breadth of the claims which fail to recite critical feature of the invention as it relates structure to function, undue experimentation would be required of the skilled artisan to make or use the claimed invention as claimed. Therefore, it would require undue experimentation to practice this invention as claimed, because the skilled artisan would have no reasonable expectation that claimed $\sigma 1\beta$ receptor variants could be made and used for any specific purpose. Further the nucleic acids that comprise variants of SEQ ID NO:1 or encode variants of the polypeptide of SEQ ID NO:2 may not specifically hybridize to the polynucleotide of SEQ ID NO:1 or to the polynucleotide that encodes the polypeptide of SEQ ID NO:2. Applicant has not disclosed how to use said nucleic acids that do not specifically hybridize to the polynucleotide of SEQ ID NO:1. Further the specification does not disclose how to use nucleic acids that comprise variants of SEQ ID NO:1 or encode fragments or variants of the polypeptide of SEQ ID NO:2 without functional activity.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to make and use the invention. As is evidence in the discussions *supra*, each of *Wands* factors has been carefully considered in the instant grounds of rejection, and it is maintained that undue experimentation would be required by the skilled artisan to make and use the instant invention.

Further, the vector comprising the claimed nucleic acid, the cell comprising said vector, the cell comprising said nucleic acid, and the method of producing polypeptide encoded by claimed nucleic are also rejected under 35 U.S.C. 112, first paragraph, for the reason given above.

Claim Rejection 35 USC § 112, 1st paragraph (Written Description)

6. Claims 6, 7 (original), claims 1, 5 and 11 (amended) and claims 33, 34 (newly added) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues that the structure of the invention has clearly been established and one of skill in the art could readily predict the structure as claimed. Applicant also argues that the codon usage of the claimed variants can be selected depending on the desired properties and in accordance with the host organism or cell. Also argued is that the person of skill in the art can readily envision active variants of SEQ ID NO:1 and 2. Applicant's arguments have been fully considered but are not found persuasive.

The court and the Board have repeatedly held (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*,18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the

invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. Also, where a claim purports to cover all nucleic acids that encode a specific protein and the specification discloses but a single DNA known to do so, the situation is analogous to a single means claim and does not meet the enablement requirement under para. 1 of §112. The court has also held that a claimed nucleic acid could meet the written description and enablement requirements if the nucleic acid were defined by a disclosed process found, after-the-fact, to produce the nucleic acid, and claimed as a product-by-process. However, in the instant case, the nucleic acids are not claimed as a product-by-process, nor does the specification disclose any process known to yield a claimed nucleic acid.

The only difference between the cases reviewed by the court and Board, and the instant case, is that in addition to recitation of the desired protein activity, the claims also recite a broad arbitrary structural relationship between the claimed nucleic acid sequence, either in terms of its nucleotide sequence or the polypeptide encoded, and the single disclosed species of nucleotide sequence and amino acid sequence, respectively. Consequently, the claims do not purport to claim *all* nucleotide sequences, which encode a particular functional protein. However, this distinction does not aid Applicant's cause. The recited structural relationships are arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level; and the specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to the recited nucleotide sequence or that encodes a polypeptide that is not 100% identical to the recited amino acid sequence.

While one of skill in the art can readily envision in numerable species of nucleic acid sequences that are at least a given % identity to a reference nucleotide sequence and that encode a polypeptide at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide classified as $\sigma 1\beta$ receptor. The fact remains that the actual nucleic acid sequences which encode a protein classified as $\sigma 1\beta$ receptor or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship

with a known functional sequence. For example, if one skilled in the art were to make a synthetic nucleotide sequence that encoded a $\sigma 1\beta$ receptor with 85% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a $\sigma 1\beta$ receptor than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature.

To put the situation in perspective, the number of possible amino acid sequences of 100 amino acids in length is 20^{100} (approx. 10^{130}) and the number of possible nucleotide sequences of 300 nucleotides in length is 4^{300} (approx. 4×10^{180}) . The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \ldots + X^{n-1}L(L-1)(L-2)\ldots(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)\ldots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids).

For a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where $n<<L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26}. For a 300 nucleotide reference sequence, the number of possible 300 nucleotide sequences that are at least 90% identical to the reference is approximately 1.6×10^{56}.

In the present case, the reference amino acid sequence, SEQ ID NO:2 is 192 amino acids long, and the reference nucleotide sequence, SEQ ID NO:1 is 597 nucleotides long. Using the approximation formula, the number of possible amino acid sequences and nucleotide sequences that are at least 85% identical to the reference amino acid sequence or nucleotide sequence, would be billions. While limiting the scope of potential sequences to those that are at least 85% identical to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. All of these values greatly exceed the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those, which encode a $\sigma 1\beta$ receptor. Therefore, inclusion of the

structural relationships in the claim does not distinguish the instant fact situation from those reviewed in *Amgen, Fiers,* and *Regents of the Univ. Calif.*

The specification does not provide any information on what amino acid residues are necessary and sufficient for $\sigma 1\beta$ receptor activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a $\sigma 1\beta$ receptor polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there are no other examples of a as $\sigma 1\beta$ receptor known that have structural homology with SEQ ID NO:2, with same ligand specificity and activity, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. Furthermore, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case

here, where specification discloses only one putative functional amino acid sequences, SEQ ID NO:2, for a polypeptide having the necessary properties for the disclosed uses, and provides no guidance on obtaining polypeptide variants of SEQ ID NO:1, which would be suitable.

The claims also encompasses nucleic acid comprising fragments (variants) of SEQ ID NO:1 or fragments (variants) encoding the polypeptide of SEQ ID NO:2 encoding variants of the protein disclosed in SEQ ID NO:2, said variants may be completely unrelated, structurally and functionally to the protein encoded by SEQ ID NO:1 .

The common function of the nucleic acid (SEQ ID NO:1) encoding the polypeptide (SEQ ID NO:2), which is based upon a common property or critical technical feature of the genus claimed is not disclosed. The claims, as written, encompass nucleic acids encoding polypeptides, which vary substantially in length and also in amino acid composition. The instant disclosure of a polynucleotide of SEQ ID NO:1 encoding the polypeptide of SEQ ID NO:2 does not adequately describe the scope of the use of the claimed genus, which encompasses a substantial variety of subgenera including polynucleotides encoding full-length proteins, comprising fragments of SEQ ID NO:1 or variants encoding polypeptides classified as $\sigma 1\beta$ receptor, chimeric constructs, fusion constructs, which may encode polypeptides completely, unrelated functionally to the polypeptide of SEQ ID NO:2. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features

constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Instant specification fails to provide sufficient descriptive information, such as definitive structural and functional features of the claimed genus of polypeptides. There is no description of the conserved regions, which are critical to the structure, and function of the genus claimed. For example, what regions and fragments of the claimed $\sigma 1\beta$ receptor contain a definitive structural feature required for protein function? The specification proposes to discover other members of the genus by using screening assays and techniques involving probes, primers, and hybridization. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed. No identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific polypeptide and nucleotide sequences and the inability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe, enable and

use the genus as broadly claimed. The skilled artisan cannot envision the detailed chemical structure of the encompassed proteins and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. It is acknowledged that the skill of the artisan in the molecular biology art is high. However, in the current instance, **there is no clear evidence of activity possessed by the claimed genus of nucleic acid molecules encoding variant $\sigma 1\beta$ receptor polypeptides, the critical special technical feature of the polypeptides or how the critical special technical feature encompassed by the genus claimed relates to function.** Because of the lack of guidance in the prior art and current application, one skilled in the art could not predict if the variants $\sigma 1\beta$ receptor have the same activity as the protein disclosed in SEQ ID NO:2, since no activity is disclosed, or if they contain the domain(s) of SEQ ID NO:2, containing the critical special technical feature of the claimed $\sigma 1\beta$ receptor, since no critical special technical feature is disclosed.

The skilled artisan cannot envision the detailed chemical structure of the encompassed compounds and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with

reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid or polypeptide is itself is required. See *Fibers v. Revel*, 25 USPQ d. 1601 at 1606 (CAFC 1993) and *Amen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus of nucleic acids by only their functional activity, does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Therefore the specification fails to disclose the activity of the claimed genus of $\sigma 1\beta$ receptor, the critical special technical

feature of the polypeptides or how the critical special technical feature encompassed by the fragments and variants of claimed $\sigma 1\beta$ receptor relates to function.

The claims encompass nucleic acids encoding proteins, which are structurally and functionally unrelated to the protein/nucleic acid disclosed in SEQ ID NO:2 and 1, respectively. Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of nucleic acids . There is no description of the conserved regions, which are critical to the structure, and function of the genus claimed. The claimed nucleic acid encodes an orphan $\sigma 1\beta$ receptor whose activity has not been disclosed. The complexity of assigning a function and membership into a the genus of $\sigma 1$ receptors is highlighted by the diverse function/compound specificity of $\sigma 1\beta$ receptors disclosed above (IDS). Neither the claims nor the specification disclose what specific biological activity is associated with the claimed $\sigma 1\beta$ receptor or the special technical feature encompassed by specific domains associated with a specific activity of the claimed genus. The superfamily of $\sigma 1$ receptor are specialized proteins designed for chemical recognition of ligands, and subsequent transduction of information encoded in those ligands/compounds to the machinery of the cell. The $\sigma 1$ receptor interacts with many diverse compounds having diverse effects. The important features, which would help to define the $\sigma 1\beta$ receptor activity and define the genus claimed, have not been disclosed in the specification nor prior art. Further the activity transduced is not disclosed or how it relates structure to function.

The claims encompass nucleic acids encoding proteins, which are structurally and functionally unrelated to the protein of SEQ ID NO:2. Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of polypeptides. There is no description of the conserved regions, which are critical to the structure, and function of the genus claimed. Further, the vector comprising the claimed nucleic acid, the cell comprising said vector, the cell comprising said nucleic acid, and the method of producing polypeptide encoded by claimed nucleic are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 33 is rejected under 35 U.S.C. 102(b) as being anticipated by Malliga et al (See IDS, The Journal of Pharmacological and Experimental Therapeutics, Vol. 289, page 251-260).

Malliga discloses transformed Jurkat T lymphocyte cells containing the polynucleotide of claim. Although the cells are not transformed with the polynucleotide of claim 1, the cells disclosed are transformed with some other polynucleotide. Jurkat T lymphocyte cells meet the limitations of claim 33 because they inherently contain the cDNA polynucleotide of claim 1, absent evidence to the contrary.

No claim is allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nirmal S. Basi
Art Unit 1646
June 8, 2004

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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